

Remarks

Reconsideration of this Application is respectfully requested.

Status of the Claims

Upon entry of the foregoing amendments, claims 1-22 are pending in the application, with claims 1 and 15 being the independent claims. Claim 1 is sought to be amended. New claims 2-22 are sought to be added. Support for the foregoing amendments can be found throughout the specification, specifically at pages 16-26. Hence, these amendments introduce no new matter, and their entry and consideration are respectfully requested.

Based on the foregoing amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Drawings

Applicant respectfully submits that a complete set of drawings, numbered 1-12, were filed with the present application. (A copy of the USPTO date-stamped post card acknowledging receipt of Figures 1-12 is attached.) Applicants also note that Figures 1-12 are currently available on the Public Patent Application Information Retrieval access site. In addition, U.S. Published Patent Application No. 2004/0086968, corresponding to the present application, published with all of Figures 1-12. Hence, Applicant respectfully requests that this objection be reconsidered and withdrawn. In the event that

the Examiner is still unable to locate a complete set of Figures 1-12, Applicant will gladly provide a second copy.

Objection to the Specification

The Examiner has objected to the specification because descriptions of Figures 1-4 appear in "Brief Description of the Figures". As noted above, Applicant respectfully submits that Figures 1-4 were filed with the present application, and that the figure descriptions are therefore appropriate. Applicant respectfully requests that this objection be reconsidered and withdrawn.

Rejections under 35 U.S.C. §112, First Paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art to which it pertains, that the inventor, at the time the application was filed, had possession of the invention.

Present claim 1 recites:

A nucleic acid molecule encoding a mutant *Aequorea victoria*
Green Fluorescent Protein, the mutant Green Fluorescent Protein mutated
at amino acid positions corresponding to the amino acid residues at
positions 64 and 65 of SEQ ID NO:4;

wherein the residue at position 64 is alanine, valine, leucine, isoleucine, proline, methionine, glycine, serine, threonine, cysteine, alanine, asparagine, glutamine, aspartate, or glutamate; and

wherein the residue at position 65 is alanine, glycine, threonine, cysteine, asparagine, or aspartate;

with the provisos that

if the residue at position 64 is leucine then the residue at position 65 is not alanine, glycine, cysteine, or threonine;

if the residue at position 64 is valine then the residue at position 65 is not alanine;

if the residue at position 64 is methionine then the residue at position 65 is not glycine; and

if the residue at position 64 is glycine then the residue at position 65 is not cysteine.

Applicant submits that the mutants of *Aequorea victoria* Green Fluorescent Protein recited in present claim 1 (and newly added claims 2-22) are fully described in the present specification. Hence, one skilled in the art of protein engineering would reasonably conclude that that inventor was in full possession of the presently claimed invention.

Applicant also respectfully submits that clearly more than two species of mutants are disclosed in the application. At a minimum, the present specification discloses seven mutants listed in Table 3 (Green Lantern-2/A1, Green Lantern-2/A2, Green Lantern-2/A3, Green Lantern-2/A4, Green Lantern-2/A5, Green Lantern-2/A8, and Green Lantern-2/A9). Applicant therefore asserts that as the subject matter of present claim 1 has clear criteria that one skilled in the relevant arts would conclude was conceptualized and practiced by the inventor as demonstrated by the seven illustrative species of Table 3. The subject matter of claim 1 has therefore been described in the specification in a manner that conveys to one skilled in the relevant arts that the inventor had possession of the invention, and thus claim 1 meets the written description requirement of 35 U.S.C. § 112, first paragraph. Applicant therefore respectfully requests that the rejection be reconsidered and withdrawn.

Claim 1 also stands rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, to make and use the invention. Applicant respectfully submits, as the Examiner has indicated on page 8 of the Office Action, mutant GFPs that differ from the wild type *A. victoria* GFP by mutations at positions 64 and 65 are enabled by the present specification. In accordance with this, Applicant submits that present claim 1 clearly complies with the enablement requirement of 35 U.S.C. 112, first paragraph. Applicant therefore respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph

Claim 1 stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In present claim 1, the Green Fluorescent Protein is identified in the claim as that of the species *Aequorea victoria*, and the mutated residues are localized to positions 64 and 65 of SEQ ID NO:4. Hence, Applicant submits that present claim 1 is not indefinite. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Rejection under 35 U.S.C. §102(b)

The Examiner has rejected claim 1 as being allegedly anticipated under 35 U.S.C. § 102(b) by Delagrave *et al.*, *Bio/Tech.* 13:151-154 (1995) (hereinafter "Delagrave"). Applicant respectfully traverses this rejection.

Applicant respectfully submits that Delagrave does not disclose the nucleic acid molecules of the present invention, and hence, Delagrave does not disclose every element of present claim 1. Therefore, present claim 1 is not anticipated under 35 U.S.C. § 102(b). Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103(a)

The Rejection over Delagrave

The Examiner has rejected claim 1 as allegedly obvious over Delagrave under 35 U.S.C. §103(a). Applicant respectfully traverses this rejection.

Present claim 1 is directed to GFP proteins having particular mutations at positions 64 and 65 that are not disclosed in Delagrave. Specifically, Delagrave does not disclose that residues at both positions be mutated simultaneously, that the residue at position 64 does not have an aromatic side chain, and that the residue at position 65 does not have a side chain longer than 2 carbons. Hence, Delagrave is seriously deficient as a primary reference on which to base a *prima facie* case of obviousness.

Applicants have found that the presently claimed modifications to the GFP sequence result in mutants with fluorescence as high or higher than the wild-type *A. victoria* GFP (Table 3). This is surprising and nonobvious because the wild-type GFP has an aromatic amino acid (phe) at position 64 and the previously identified mutant GFP having enhanced fluorescence known as "Green Lantern-1" also has phenylalanine at position 64. In addition, the criteria of having an amino acid side chain with a short chain length was not previously recognized. Thus, the invention relies on the recognition that when these two conditions are met simultaneously in a GFP mutant, the fluorescence properties of GFP can be improved. Because Delagrave does not provide motivation for making GFP mutants by substituting this subset of amino acids at positions 64 and 65, the invention is nonobvious under 35 U.S.C. §103(a). Applicant therefore respectfully requests that this rejection be reconsidered and withdrawn.

The Rejection Over Cormack

The Examiner has also rejected claim 1 as allegedly obvious over Cormack et al. (U.S. Patent 5,804,387; hereinafter "Cormack") 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce double GFP mutants comprising S65T or S65A coupled with any amino acid substituted for F64. Applicant disagrees that these modifications, and in particular the mutants at positions 64 and 65 recited in claim 1, are disclosed in Cormack.

The presently claimed invention is directed to mutations made at positions 64 and 65, namely that residues at both positions can be mutated simultaneously, that the residue at position 64 does not have an aromatic side chain, and that the residue at position 65 does not have a side chain longer than 2 carbons. Cormack does not provide motivation for making the set of mutations set forth in present claim 1. Hence, Applicant respectfully submits that the present claims are nonobvious under 35 U.S.C. § 103(a). Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

Double Patenting

The Examiner has rejected claim 1 under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-3 and 14 of U.S. Patent No. 6,638,732. Applicant respectfully requests that the nonstatutory double patenting rejection be held in abeyance and addressed when allowable subject matter has been determined.

Other Matters

Applicant thanks the Examiner for returning the initialed and signed Form PTO-1449s with the current Office Action. Applicant notes, however, that the Examiner did not initial off on Document AL2 (WO 02/085936) on page 2 of Applicant's Second Supplemental Information Disclosure Statement. Applicant respectfully requests that the Examiner provide an initialed and signed copy of this page of the Second Supplemental Information Disclosure Statement with the Examiner's next communication, indicating that this reference has been considered.

Conclusion

All of the stated grounds of objection and rejection have been addressed. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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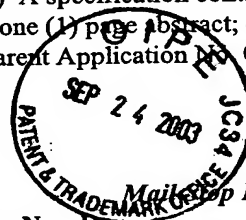
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For: Mutants of Green Fluorescent Protein

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. PTO Fee Transmittal (Form PTO/SB/17);
3. PTO Utility Patent Application Transmittal (Form PTO/SB/05);
4. Authorization to Treat a Reply As Incorporating An Extension of Time Under 37 C.F.R. § 1.136(a)(3);
5. PTO-2038 Credit Card Payment Form in the amount of \$750.00 to cover the Filing fee for the patent application;
6. Rule 53(b) Continuation U.S. Utility Patent Application entitled: **Mutants of Green Fluorescent Protein**; and naming as inventor: Krista EVANS; the application consisting of: a) Application Data Sheet; b) A copy of the Declaration executed by Krista EVANS on November 24, 1998 (2 pages), as filed in the parent Application No. 09/472,065, and as originally filed in 35 U.S.C. § 120 priority U.S. Appl. No. 08/970,762; c) A specification containing: (i) 37 pages of description prior to the claims; (ii) 1 page of claims (1 claim); and (iii) a one (1) page abstract; d) 11 pages of a paper copy of the Substitute Sequence Listing filed on April 24, 2001, in the parent Application No. 09/472,065, filed December 23, 1999; and e) 12 sheets of formal drawings (Figures 1-12);
7. Request to Open New Disk File; and
8. Two (2) return postcards.



For Advance Notification of Application Number

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